

CORRECTED VERSION

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:  
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21. Jan. 2005

Frist: 06.03.05 PA

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT AND  
THE WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY, OR THE DECLARATION

B2	
B3	
Sekr	1161
EDV	
Ablg.	

(PCT Rule 44.1)

Date of mailing (day/month/year)	06/12/2004
FOR FURTHER ACTION	See paragraphs 1 and 4 below

Applicant's or agent's  
file reference  
C62677PC

International application No.  
PCT/EP2004/003163

International filing date  
(day/month/year) 25/03/2004

Applicant  
CYTOS BIOTECHNOLOGY AG

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.  
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 65 epo.nl  
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Authorized officer

Maria Brandt

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>C62677PC</b>	<b>FOR FURTHER ACTION</b>		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. <b>PCT/EP2004/003163</b>	International filing date (day/month/year) <b>25/03/2004</b>	(Earliest) Priority Date (day/month/year) <b>26/03/2003</b>	
Applicant  <b>CYTOS BIOTECHNOLOGY AG</b>			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☒ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☒ Unity of invention is lacking (see Box III).

**4. With regard to the title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. With regards to the drawings,**

a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2004/003163

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
  - a. type of material
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing.
  - b. format of material
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing
    - ☒ contained in the international application as filed
    - ☐ filed together with the international application in computer readable form
    - ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/003163

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K39/39 A61K39/12 C07K14/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 03/024481 A (BACHMANN MARTIN F ; LIPOWSKY GERAD (CH); MAURER PATRICK (CH); MEIJERIN) 27 March 2003 (2003-03-27) the whole document	1-103
P,Y	WO 2004/000351 A (RENNER WOLFGANG A ; BACHMAN MARTIN F (CH); CYTOS BIOTECHNOLOGY AG (CH)) 31 December 2003 (2003-12-31) the whole document	1-103



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 November 2004

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Giebeler, K

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/003163

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>NOTKA FRANK ET AL: "Accelerated clearance of SHIV in rhesus monkeys by virus-like particle vaccines is dependent on induction of neutralizing antibodies" VACCINE, vol. 18, no. 3-4, 23 September 1999 (1999-09-23), pages 291-301, XP002291383 ISSN: 0264-410X see especially abstract and Figure 1; the whole document</p>	1-103
Y	<p>MARTIN SEAMUS J ET AL: "Immunization of human HIV-seronegative volunteers with recombinant p17/p24:Ty virus-like particles elicits HIV-1 p24-specific cellular and humoral immune responses" AIDS (PHILADELPHIA), vol. 7, no. 10, 1993, pages 1315-1323, XP009034714 ISSN: 0269-9370 see especially abstract and page 1316, column 1, paragraph 4 and column 2; the whole document</p>	1-103
Y	<p>LUO LIZHONG ET AL: "Induction of V3-specific cytotoxic T lymphocytes responses by HIV gag particles carrying multiple immunodominant V3 epitopes of gp120" VIROLOGY, vol. 240, no. 2, 20 January 1998 (1998-01-20), pages 316-325, XP002291384 ISSN: 0042-6822 see especially abstract, Figure 1, and page 323, column 2, paragraph 2; the whole document</p>	1-103
Y	<p>GERBER S ET AL: "Human papillomavirus virus-like particles are efficient oral immunogens when coadministered with Escherichia coli heat-labile enterotoxin mutant R192G or CpG DNA" JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 75, no. 10, May 2001 (2001-05), pages 4752-4760, XP002246338 ISSN: 0022-538X the whole document</p>	21, 26-47, 68,72-92
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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STORNI TAZIO ET AL: "Critical role for activation of antigen-presenting cells in priming of cytotoxic T cell responses after vaccination with virus-like particles" JOURNAL OF IMMUNOLOGY, vol. 168, no. 6, 15 March 2002 (2002-03-15), pages 2880-2886, XP002291385 ISSN: 0022-1767 the whole document	21-23, 26-47, 68,69, 72-92
Y	WO 00/39304 A (CHIRON CORP) 6 July 2000 (2000-07-06) see especially pages 32-38 the whole document	1-103
Y	ADDI M M ET AL: "Comprehensive epitope analysis of human immunodeficiency virus type 1 (HIV-1)-specific T-cell responses directed against the entire expressed HIV-1 genome demonstrate broadly directed responses, but no correlation to viral load." JOURNAL OF VIROLOGY, vol. 77, no. 3, February 2003 (2003-02), pages 2081-2092, XP002291386 ISSN: 0022-538X see especially Tables 4 and 5; the whole document	1-103
Y	BUONAGURO L ET AL: "High efficient production of Pr55gag virus-like particles expressing multiple HIV-1 epitopes, including a gp120 protein derived from an Ugandan HIV-1 isolate of subtype A" ANTIVIRAL RESEARCH, vol. 49, no. 1, January 2001 (2001-01), pages 35-47, XP002304514 ISSN: 0166-3542 the whole document	1-103
Y	JEGERLEHNER ANDREA ET AL: "A molecular assembly system that renders antigens of choice highly repetitive for induction of protective B cell responses" VACCINE, vol. 20, no. 25-26, 19 August 2002 (2002-08-19), pages 3104-3112, XP002291387 ISSN: 0264-410X see especially abstract the whole document	12-17, 60-65

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/003163

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03024481	A	27-03-2003	EP 1450856 A2	01-09-2004
			WO 03024481 A2	27-03-2003
			US 2003099668 A1	29-05-2003
WO 2004000351	A	31-12-2003	WO 2004000351 A1	31-12-2003
			US 2004005338 A1	08-01-2004
WO 0039304	A	06-07-2000	AU 2221600 A	31-07-2000
			AU 2487300 A	31-07-2000
			AU 2596600 A	31-07-2000
			CA 2358385 A1	06-07-2000
			CA 2358915 A1	06-07-2000
			CA 2360347 A1	06-07-2000
			EP 1433851 A2	30-06-2004
			EP 1141313 A2	10-10-2001
			EP 1141314 A2	10-10-2001
			EP 1141315 A2	10-10-2001
			JP 2002533124 T	08-10-2002
			JP 2002533125 T	08-10-2002
			JP 2003523721 T	12-08-2003
			WO 0039302 A2	06-07-2000
			WO 0039303 A2	06-07-2000
			WO 0039304 A2	06-07-2000
			US 2003223964 A1	04-12-2003
			US 6602705 B1	05-08-2003
			US 2002146683 A1	10-10-2002
			ZA 200105589 A	06-08-2002
			ZA 200105590 A	16-05-2002

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2004/003163

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
  
1-103 (all partially)
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



PCT/EP2004/003163

## SUMMARY OF FACTS AND SUBMISSIONS

- I. A form PCT/ISA/206 was issued on 31/08/04 informing the applicant that the application did not comply with the requirements of unity of invention (Rule 13.1-13.3 PCT). It was considered that there were a total of 33 groups of inventions claimed in the international application. The applicant was invited to pay 32 additional search fees.
- II. In response, the applicant paid one further fee for group no. 15.

## RESULTS OF THE PRIOR REVIEW

1. Under Rule 40.2, first sentence, PCT, when an additional fee is paid under protest, the case is subject to a "prior review of the justification for the invitation to pay an additional fee".
2. In his letter dated 30/09/04, the applicant argues that "the Examiner seemingly considers Alum, incomplete or complete Freud's adjuvant" disclosed within the documents referred to in form PCT/ISA/206 "as immunostimulatory substances in accordance with the present invention. The latter are, however, classical adjuvants" (page 1, last paragraph). Furthermore, the applicant submits that "[t]he provision of compositions comprising an HIV polypeptide bound to a virus-like particle to which is bound, or preferably which is packaged (see e.g. claim 84) with, at least one immunostimulatory nucleic acid" (page 4, second paragraph) is to be regarded as special technical feature giving rise to a single inventive concept.
3. After a prior review of the opinion expressed in form PCT/ISA/206, the objection to lack of unity has been found to be justified.


Concerning the adjuvants alum, incomplete or complete Freud's adjuvant disclosed in the prior art cited in form PCT/ISA/206, there is no reason to believe that these are not covered by the general term "immunostimulatory substances" used in claim 1. On page 16, lines 8-10, of the description of the application, the term "immunostimulatory substance" is defined as any "substance capable of inducing and/or enhancing an immune response", which also applies to adjuvants. Moreover, immunostimulatory nucleic acids such as synthetic oligodeoxynucleotides containing unmethylated CpG dinucleotide motifs have been described in the prior art as "promising mucosal adjuvant" (see the document J.


VIROL. 75 (2001) 4752-4760 by Gerber et al. cited in the Partial International Search Report, in particular page 4754, column 1, lines 1-9). This means that preferred immunostimulatory substances according to the present application are also adjuvants, and there is no contradiction if an immunostimulatory substances has adjuvant properties. Page 20, line 28 to page 21, line 6 of the description, to which the applicant refers in his letter, does also not contradict said definition of the term "immunostimulatory substance".


Page 16, lines 10-15 of the description further states that "immunostimulatory substances, as used herein, include, but are not limited to, toll-like receptor activ[at]ing substances and substances inducing cytokine secretion. Toll-like receptor activating substances include, but are not limited to, immunostimulatory nucleic acids, peptidoglycans, lipopolysaccharides, lipoteichonic acids, imidazoquinoline compounds, flagellins, lipoproteins, and immunostimulatory organic substances such as taxol", and makes clear that the invention includes, but is definitely not limited to immunostimulatory nucleic acids as immunostimulatory substances.

According to Rule 13.2 PCT, the expression "special technical feature" shall mean those features that define a contribution which each of the **claimed** inventions, considered as a whole, makes over the prior art. The presence of an immunostimulatory nucleic acid (a preferred embodiment according to claims 26 to 47) is not a mandatory feature of the **claimed** inventions as indicated in form PCT/ISA/206, and does, therefore, not represent a special technical feature linking the claimed inventions.

4. The applicant is therefore invited to pay a protest fee (Rule 40.2(e) PCT), should he desire further examination of the protest made (pursuant to Rule 40.2(e) PCT).

  
C. Gugerell

  
K. Giebler

  
C. Donath